PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/NO2004/000335	05.11.2004	06.11.2003

International Patent Classification (IPC) or both national classification and IPC
A61K51/08, A61K49/00, A61P9/00, A61P9/06, A61P11/00, A61P1/16, A61P9/10

Applicant
AMERSHAM HEALTH AS

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/NO2004/000335

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-11 in part

because:

☒ the said international application, or the said claims Nos. 10 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1-11 in part

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☒ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-11 in part

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,5,11
	No:	Claims	1-3,6,8-10
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-11
Industrial applicability (IA)	Yes:	Claims	1-9,11
	No:	Claims	10

2. Citations and explanations

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item III.

Claim 10 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV.

The separate inventions/groups of inventions are:

No.	Claims	Subject
1.	1-11 in part	Pharmaceutical according to claims 1-8, kit according to claim 11, and their use in a method of diagnosis and/or treatment of heart failure.
2.	1-9 and 11 in part	Pharmaceutical according to claims 1-8, kit according to claim 11, and their use in a method of diagnosis and/or treatment of cardiac arrhythmias
3.	1-11 in part	Pharmaceutical according to claims 1-8, kit according to claim 11, and their use in a method of diagnosis and/or treatment of COPD.
4.	1-11 in part	Pharmaceutical according to claims 1-8, kit according to claim 11, and their use in a method of diagnosis and/or treatment of liver fibrosis.
5.	1-11 in part	Pharmaceutical according to claims 1-8, kit according to claim 11, and their use in a method of diagnosis and/or treatment of atherosclerosis.

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The problem underlying the present application is to provide agents for (radio)imaging and/or (radio)diagnosis of several diseases. As a solution to these problems, labelled angiotensin II analogues are proposed, all containing the sequence as defined in present claim 1. Besides the presence of this sequence requirement, the common technical feature may also be found in the fact, that of the diseases to be diagnosed it is said that

fibrosis is prominent.
In the prior art, labelled angiotensin II analogues have already been used for detecting and/or imaging its receptors.
WO 98/18496 A claims similarly labelled peptides. Heart failure is mentioned in the first paragraph of page 2. The first paragraph of page 6 gives the required sequence: Arg-Val-Tyr-Ile-His-Pro = RVYIHP.
WO 02/064734 A describes radiolabelling of identical or similar peptides. The sequence VYIHP est present in sequences 159 and 162-165.
In WO 97/10852 A, the sequence VYIHP is present in the sequences of claims 5 and 13. It also contains a the chelating group, though different from the one defined in claims 4-5.
In DE 195 36 783 A1, the sequence VYIHP is present in example 5, and in the claims.
Several documents describe a labelled peptide, in which X1=Sar, X2=Arg, X3=Ile, L is absent, and Z=125I.
In JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, vol. 36, no. 5 Supplement 1, 2000, pages S395-S396, XP008054675 ISSN: 0160-2446, it is used for detecting changes in the intimal smooth muscle layer of human atherosclerotic coronary arteries.
In CELLULAR AND MOLECULAR NEUROBIOLOGY, vol. 13, no. 3, 1993, pages 233-245, XP008054685 ISSN: 0272-4340, it is used for detecting Angiotensin II receptors in bovine retinal microvessels.
In NEUROENDOCRINOLOGY, vol. 44, no. 1, 1986, pages 15-21, XP008054687 ISSN: 0028-3835, it is used for imaging angiotensin II receptors in brain.
In BIOMEDICAL RESEARCH, vol. 9, no. 1, 1988, pages 27-31, XP008054681 ISSN: 0388-6107, it is used for imaging angiotensin II binding sites in the human adrenal gland.
In BRAIN RESEARCH, vol. 326, no. 1, 1985, pages 137-143, XP008054668, it is used for imaging angiotensin II receptors in the canine CNS.

Thus, not only the peptide sequence and its use in imaging is known to the skilled person. Indeed, the same sequence has also been used in or suggested for at least one of the diseases falling under the concept of "diseases where fibrosis is prominent", as defined in the present application.
Therefore, the concept of using the specified sequence(s) in the detection/imaging of "diseases where fibrosis is prominent" can no longer be used as "special technical feature in the sense of Rule 13 PCT, since it has already been disclosed in the prior art.
Since there is no other technical feature, that could fulfil the role of special technical

feature in the sense of Rule 13 PCT, the present application lacks unity of invention, containing the subject-matters as listed.
As searching the remaining subjects would have caused a major supplementary effort in searching and/or in formulating the Written Opinion of the International Searching Authority, a search has been performed for the first subject only. The following is limited accordingly.
Although some document cited in the present search report may also be pertinent for further inventions mentioned this does not imply, that the search for those subjects has been fully performed.

Re Item V.

1 Reference is made to the following document:

D1: WO 98/18496 A (NYCOMED IMAGING AS; COCKBAIN, JULIAN; KLAVENESS, JO; NAEVESTAD, ANNE;) 7 May 1998 (1998-05-07)

D2: WO 02/064734 A (PALATIN TECHNOLOGIES, INC; SHARMA, SHUBH, D; SHI, YI-QUN) 22 August 2002 (2002-08-22)

D3: WO 97/10852 A (INSTITUT FUER DIAGNOSTIKFORSCHUNG GMBH AN DER FREIE; DINKELBORG, LUDGE) 27 March 1997 (1997-03-27)

D4: DE 195 36 783 A1 (INSTITUT FUER DIAGNOSTIKFORSCHUNG GMBH AN DER FREIEN UNIVERSITAET BERL) 27 March 1997 (1997-03-27)

**D5: Katugampola Sidath D et al: "Changes in ETA-, AT1- and AT2-receptors in the phenotypically transformed intimal smooth muscle layer of human atherosclerotic coronary arteries"
Journal of Cardiovascular Pharmacology, vol. 36, no. 5, Supplement 1, 2000, pages S395-S396, XP008054675 ISSN: 0160-2446**

**D6: Sato Takaya et al: "Quantitative receptor autoradiographic analysis for angiotensin II receptors in bovine retinal microvessels: Quantitation with radioluminography"
Cellular And Molecular Neurobiology, vol. 13, no. 3, 1993, pages 233-245, XP008054685 ISSN: 0272-4340**

D7: Healy D P et al: "LOCALIZATION OF CENTRAL ANGIOTENSIN II RECEPTORS

WITH IODINE-125 SAR-1 ILE-8-ANGIOTENSIN II PERIVENTRICULAR SITES OF THE ANTERIOR THIRD VENTRICLE"
Neuroendocrinology, vol. 44, no. 1, 1986, pages 15-21, XP008054687 ISSN: 0028-3835

D8: Shigematsu K et al: "Autoradiographic evidence of angiotensin II binding sites in the human adrenal gland"
Biomedical Research, vol. 9, no. 1, 1988, pages 27-31, XP008054681 ISSN: 0388-6107

D9: Speth R C et al: "Angiotensin II receptor localization in the canine CNS"
Brain Research, vol. 326, no. 1, 1985, pages 137-143, XP008054668

D10: Bagby Susan P et al: "ANG II AT(1) and AT(2) receptors in developing kidney of normal microswine."
American Journal of Physiology. Renal Physiology, vol. 283, no. 4, October 2002 (2002-10), pages F755-F764, XP002354300 ISSN: 0363-6127

D11: Serneri G G et al: "Cardiac angiotensin II formation in the clinical course of heart failure and its relationship with left ventricular function."
Circulation Research, vol. 88, no. 9, 11 May 2001 (2001-05-11), pages 961-968, XP002354301 ISSN: 1524-4571

D12: WO 03/051859 A (AMERSHAM PLC; BOUVET, DENIS, RAYMOND, CHRISTOPHE; WADSWORTH, HARRY, JO) 26 June 2003 (2003-06-26)

D13: WO 03/006491 A (AMERSHAM HEALTH AS; CUTHBERTSON, ALAN; INDREVOLL, BAARD; SOLBAKKEN, MA) 23 January 2003 (2003-01-23)

D14: WO 03/006070 A (AMERSHAM PLC; ARCHER, COLIN, MILL; WADSWORTH, HARRY, JOHN; ENGELL, TOR) 23 January 2003 (2003-01-23)

D15: Heppeler A et al: "RECEPTOR TARGETING FOR TUMOR LOCALISATION AND THERAPY WITH RADIOPETIDES"
Current Medicinal Chemistry, Bentham Science Publishers BV, BE, vol. 7, no. 9, 2000, pages 971-994, XP000982225 ISSN: 0929-8673

D16: HENZE M et al: "PET imaging of somatostatin receptors using"
Journal of Nuclear Medicine, New York, NY, US, vol. 42, no. 7, July 2001 (2001-07), pages 1053-1056, XP002245466 ISSN: 0161-5505

D17: WO 98/18498 A (MARSDEN, JOHN, CHRISTOPHER; NYCOMED IMAGING AS; KLAVENESS, JO; RONGVED) 7 May 1998 (1998-05-07)

Document **D1** discloses claims similarly labelled peptides. Heart failure is mentioned in the first paragraph of page 2. The first paragraph of page 6 gives the required sequence: Arg-Val-Tyr-Ile-His-Pro = RVYIHP
Document **D2** discloses radiolabelling of identical or similar peptides. The sequence VYIHP est present in sequences 159 and 162-165.
Document **D3** discloses radiolabelled peptides. The sequence VYIHP is present in the sequences of claims 5 and 13. However, the chelating group is different from the one defined in claims 4-5.
Document **D4** discloses radiolabelled peptides. The sequence VYIHP is present in example 5, and in the claims.
Document **D5** discloses a labelled peptide, in which X1=Sar, X2=Arg, X3=Ile, L is absent, and Z=125I. It is used for detecting changes in the intimal smooth muscle layer of human atherosclerotic coronary arteries.
In Document **D6**, the same peptide is used for detecting Angiotensin II receptors in bovine retinal microvessels.
In Document **D7**, it is used for imaging angiotensin II receptors in brain.
In Document **D8**, it is used for imaging angiotensin II binding sites in the human adrenal gland.
In Document **D9**, it is used for imaging angiotensin II receptors in the canine CNS.
In Document **D10**, it is used for imaging angiotensin II receptors in the microswine kidney.
Document **D11** uses a peptide falling within the general definition of present claim 1 for determining the influence of angiotensin II in heart failure.
Documents **D12** to **D14** disclose chelating groups of the type N4, falling under the definition of present claim 4.
Documents **D15** to **D17** disclose other useful chelators.

Present claims 1, 3, 6 and 8 do not define the chelator group, but seek protection for a radiolabelled analogue I general of the peptide sequence specified. Due to their general nature, these claims are anticipated by documents **D1** to **D10**. Therefore, claims 1,3,6 and 8 do not meet the requirements of Article 33.2 PCT for novelty.

The subject-matter of present claims 2, 9 and 10 is more specifically related to the use in the treatment and/or diagnosis of heart failure. However, the usefulness of VYIHP-

containing radiolabelled peptides in this treatment/diagnosis has already been mentioned in **D1** and **D5**. Therefore, claims 2, 9 and 10 do not meet the requirements of Article 33.2 PCT for novelty.

Moreover, **D11** uses a peptide falling within the general definition of present claim 1 for determining the influence of angiotensin II in heart failure. Starting from this document as closest prior art, the skilled person would most certainly use a labelling agent as disclosed in any of **D12** to **D14** to visualise this influence, thus arriving at the presently claimed diagnostic use. Therefore, claims 2, 9 and 10 do not meet the requirements of Article 33.3 PCT for inventive step.

The subject-matter of present claims 4, 5, 7 and 11 is limited to chelating agents. The sequence VYIHP has been disclosed in documents **D1** to **D11**, together with their affinity for the angiotensin II receptor. The compounds defined in these claims can be distinguished from this prior art by the choice of the radiolabel, which is now attached to the peptide by a chelating group. The problem to be solved is the provision of further radiolabelled angiotensin II analogues.
Yet, starting from any of **D1** to **D11** as closest prior art, the skilled person would most certainly use a labelling agent as disclosed in any of **D12** to **D14** to visualise this influence, thus arriving at the presently claimed diagnostic use. Therefore, claims 4, 5, 7 and 11 do not meet the requirements of Article 33.3 PCT for inventive step.

For the assessment of the present claim 10 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII.

Claims 1-3 and 8-11 do not meet the requirements of Article 6 PCT in that the matter for

which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved, which merely amounts to a statement of the underlying problem, without providing the technical (structural) features necessary for achieving this result.